

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: David J. Pinsky, et al.
Serial No.: Not Yet Known
Filed: Herewith
For: METHODS FOR TREATING ISCHEMIC DISORDERS
USING CARBON MONOXIDE

1185 Avenue of the Americas
New York, New York 10036
October 3, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and 37 C.F.R. §1.97, applicants would like to direct the Examiner's attention to the following publications which are listed on the attached Form PTO-1449 (**Exhibit A**). Copies of cited publications 4, 13, 23, and 38-51 are attached hereto as **Exhibits 1-16**, respectively. Publications 14-22, 24, 26-29, and 31-37 are of record in prior application U.S. Serial No. 08/721,447, filed September 27, 1996, to which priority under 35 U.S.C. §120 is claimed. Publications 1-3, 5-12, 25, and 30 are of record in prior application U.S. Serial No. 09/671,100, filed September 27, 2000, to which priority under 35 U.S.C. §120 is claimed. According to 37 C.F.R. §1.98(d), copies of

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 2

patents or publications that are of record in such prior applications need not accompany this Information Disclosure Statement.

1. U.S. Patent No. 4,885,277, Nawroth, Anticoagulant therapy, issued December 5, 1989.
2. U.S. Patent No. 5,378,464, McEver, Modulation of inflammatory responses by administration of GMP-140 or antibody to GMP-140, issued January 3, 1995.
3. U.S. Patent No. 5,839,443, Rose et al., Method for Inhibiting Thrombosis in a Patient Whose Blood is Subjected to Extracorporeal Circulation, issued November 24, 1998.
4. U.S. Patent No. 5,882,674, Herrmann, et al., Transdermal Therapeutic System Comprsing Active Substances Representing Carbon Monoxide Sources, issued March 16, 1999 (**Exhibit 1**).
5. U.S. Patent No. 6,315,995 B1, Pinsky et al., Method for Treating an Ischemic Disorder and Improving Stroke Outcome, issued November 13, 2001.
6. U.S. Patent No. 6,316,403 B1, Pinsky et al., Method for Treating an Ischemic Disorder and Improving Stroke Outcome, issued November 13, 2001.
7. U.S. Patent No. 6,391,300, Rose et al., Method for

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 3

Inhibiting Thrombosis in a Patient Whose Blood is Subjected to Extracorporeal Circulation, issued May 21, 2002.

8. WO 97/42900, Trustees of Columbia University, Rose et al., Method for Inhibiting Thrombosis in a Patient Whose Blood is Subjected to Extracorporeal Circulation, published November 20, 1997; filed May 15, 1997.
9. WO 98/13058, Trustees of Columbia University, Pinsky et al., Method for Treating an Ischemic Disorder and Improving Stroke Outcome, published April 2, 1998; filed September 25, 1997.
10. WO 99/49803, Trustees of Columbia University, Rose et al., Method for Inhibiting Thrombosis in a Patient Whose Blood is Subjected to Extracorporeal Circulation, published October 7, 1999; filed April 1, 1999.
11. WO 99/49880, Trustees of Columbia University, Pinsky et al., Method for Treating an Ischemic Disorder and Improving Stroke Outcome, published October 7, 1999; filed April 1, 1999.
12. Australian Patent No. 735258, Trustees of Columbia University, Rose et al., Method for Inhibiting Thrombosis in a Patient Whose Blood is Subjected to Extracorporeal Circulation, issued July 5, 2001.

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 4

13. U.S. Serial No. 09/671,100, Pinsky et al., Methods for Treating an Ischemic Disorder and Improving Stroke Outcome, filed September 27, 2000 (**Exhibit 2**).
14. Benedict C.R., et al. (1994) Endothelial-Dependent Procoagulant and Anticoagulant Mechanisms, Recent Advances in Understanding. Texas Heart Institute Journal 21:86-90.
15. Bronner et al. (1995) Primary prevention of stroke. The New England J. Med. 333:1392-1400.
16. Brown and Piantadosi (1992) Recovery of Energy Metabolism in Rat After Carbon Monoxide Hypoxia. J. Clin. Invest. 89:666-672.
17. Carlos and Harlan (1994) Leukocyte-Endothelial Adhesion Molecules. Blood. 24:2068-2102.
18. Connolly et al. (1996) Cerebral Protection in Homozygous Null ICAM-1 Mice After Middle Cerebral Artery Occlusion. J. Clin. Invest. 97:209-216.
19. Connolly et al. (1996) Procedural and Strain-Related Variables Significantly Affect Outcome in a Murine Model of Focal Cerebral Ischemia. Neurosurgery. 38:523-532.

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 5

20. Dawson and Snyder (1994) Gases as biological messengers; nitric oxide and carbon monoxide in the brain. J. Neuroscience. 5147-5159.
21. Dietrich et al. (1995) Influence of High-Dose Aprotinin on Anticoagulation, Heparin Requirement, and Celite-and Kaolin-Activated Clotting Time in Heparin-pretreated Patients Undergoing Open-Heart Surgery. Anesthesiology, 83(4)679-689.
22. Fassbender et al. (1995) Circulating Selectin-and Immunoglobulin-Type Adhesion Molecules in Acute Ischemic Stroke. Stroke. 26:1361-1364.
23. Fujita, T. et al., (2001) Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by derepression of fibrinolysis. Nature Medicine. 7(5):598-604 (Exhibit 3).
24. Holdright, D., et al. (1994) Comparison of the Effect of Heparin and Aspirin Versus Aspirin Alone on Transient Myocardial Ischemia and In-hospital Prognosis in Patients With Unstable Angina. J. Am. Coll. Cardiol. 24:39-45.
25. Iberti, T.J. et al., (1994) Abnormal Coagulation Profile in Brain Tumor Patients During Surgery. Neurosurgery 34:389-395.
26. Ishimaru et al. (1991) Effects of successive carbon

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 6

monoxide exposures on delayed neuronal death in mice under the maintenance of normal body temperature. Biochem. Biophys. Res. Comm. 179:836-840.

27. Jerome et al. (1994) P-selectin and ICAM-1-Dependent Adherence Reactions: Role in the Genesis of Postischemic No-Reflow. Am. J. Physiol. 226:H1316-H1321.
28. Kim et al. (1995) Adhesive Glycoproteins CD11a and Cd18 are Upregulated in the Leukocytes from Patients with Ischemic Stroke and Transient Ischemic Attacks. J. Neurol. Sci. 128:45-50.
29. Kochaneck and Hallenbeck (1992) Polymorphonuclear Leukocytes and Monocytes/Macrophages in the Pathogenesis of Cerebral Ischemia and Stroke. Stroke. 23:1367-1379.
30. Kuwabara, K. et al., (1995) Calreticulin, an Antithrombotic Agent which Binds to Vitamin K-Dependent Coagulation Factors, Stimulates Endothelial Nitric Oxide Production, and Limits Thrombosis in Canine Coronary Arteries. J. Biol. Chem. 270:8179-8187.
31. Mayevsky et al. (1995) Multiparametric monitoring of the awake brain exposed to carbon monoxide. J. Appl. Physiol. 78:1188-1196.

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 7

32. Okada et al. (1994) P-selectin and Intercellular Adhesion Molecule-1 Expression After Focal Brain Ischemia and Reperfusion. Stroke. 25:202-211.
33. Pinsky et al. (1996) Hypoxia-Induced Exocytosis of Endothelial Cell Weibel-Palade Bodies, a Mechanism for Rapid Neutrophil Recruitment After Cardiac Preservation. J. Clin. Invest. 97:493-500.
34. Schroeter et al. (1994) Local Immune Response in the Rat Cerebral Cortex After Middle Cerebral Artery Occlusion. J. Neuroimmunol. 55:195-203.
35. Seekamp et al. (1994) Role of Selectins in Local and Remote Tissue Injury Following Ischemia and Reperfusion. Am. J. Pathol. 44:592-598.
36. Tijburg et al. (1991) Activation of the coagulation mechanism on tumor necrosis factor-stimulated cultured endothelial cells and their extracellular matrix. The role of flow and Factor IX/IXa. J. Biol. Chem. 266:12067-12074.
37. Verma et al. (1993) Carbon monoxide: a putative neural messenger. Science. 259:381-384.
38. Weyrich et al. (1993) In Vivo Neutralization of P-selectin Protects Feline Heart Endothelium in Myocardial Ischemia and Reperfusion Injury. J. Clin. Invest. 91:2620-2629.

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 8

39. BBC News report, Health segment, April 30, 2001,
Deadly gas 'could save lives' (**Exhibit 4**).

40. International Search Report August 29, 1997 for
PCT/US97/08282 (**Exhibit 5**).

41. International Preliminary Examination, April 20, 1998
for PCT/US97/08282 (**Exhibit 6**).

42. Search Report October 27, 2000 from Patent Office
regarding European Patent Application No. 97926541.0
(**Exhibit 7**).

43. International Search Report, June 18, 1999 for
PCT/US99/07173 (**Exhibit 8**).

44. International Preliminary Examination, January 7,
2000 for PCT/US99/07173 (**Exhibit 9**).

45. Search Report, May 28, 2002 from Patent Office
regarding European Patent Application No. 99916264.7
(**Exhibit 10**).

46. International Search Report, February 5, 1998 for
PCT/US97/17229 (**Exhibit 11**).

47. Written Opinion September 14, 1998 for PCT/US97/17229
(**Exhibit 12**).

Applicants : David J. Pinsky, et al.
Serial No. : Not Yet Known
File : October 3, 2003
Page 9

48. International Preliminary Examination, January 8, 1999 for PCT/US97/17229 (**Exhibit 13**).

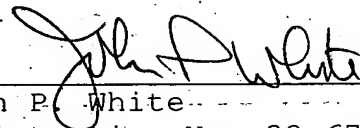
49. International Search Report, August 4, 1999 for PCT/US99/07175 (**Exhibit 14**).

50. Written Opinion February 3, 2000 for PCT/US99/07175 (**Exhibit 15**).

51. International Preliminary Examination, July 11, 2000 for PCT/US99/07175 (**Exhibit 16**).

Pursuant to 37 C.F.R. §1.97(b)(3) no fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

| | | | | | | | | | | | | | |
|--|--|---|---|---|---|-----------------|-----------------------------|-------|------------|----------------------------|-----|-------|--|
| Form PTO-1449 | | U.S. Department of Commerce Patent and Trademark Office | | | Atty. Docket No. 51917-CA-PCT-US/ JPW/GJC/DJK | | Serial No. Not Yet Known | | | | | | |
| INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) | | | | | Applicants: David J. Pinsky et al. Filing Date Herewith | | | | | | | | |
| U.S. PATENT DOCUMENTS | | | | | | | | | | | | | |
| Examiner Initial | | Document Number | | | | Date | Name | Class | Subclass | Filing Date if Appropriate | | | |
| | | 4 | 8 | 8 | 5 | 2 | 7 | 7 | 12/5/1989 | Nawroth | 514 | 15 | |
| | | 5 | 3 | 7 | 8 | 4 | 6 | 4 | 1/3/1995 | McEver | 424 | 143.1 | |
| | | 5 | 8 | 3 | 9 | 4 | 4 | 3 | 11/24/1998 | Rose et al. | 128 | 898 | |
| | | 5 | 8 | 8 | 2 | 6 | 7 | 4 | 3/6/1999 | Hermann (Exhibit 1) | 424 | | |
| | | 6 | 3 | 1 | 5 | 9 | 9 | 5 | 11/13/2001 | Pinsky et al. | 424 | 94.63 | |
| | | 6 | 3 | 1 | 6 | 4 | 0 | 3 | 11/13/2001 | Pinsky et al. | 514 | 2 | |
| | | 6 | 3 | 9 | 1 | 3 | 0 | 0 | 5/21/2002 | Rose et al. | 424 | 145.1 | |
| FOREIGN PATENT DOCUMENTS | | | | | | | | | | | | | |
| | | Document Number | | | | Date | Country | Class | Subclass | Translation | | | |
| | | | | | | | | | | Yes | No | | |
| | | 9 | 7 | 4 | 2 | 9 | 0 | 0 | 11/20/1997 | WO | | | |
| | | 9 | 8 | 1 | 3 | 0 | 5 | 8 | 4/2/1998 | WO | | | |
| | | 9 | 9 | 4 | 9 | 8 | 0 | 3 | 10/7/1999 | WO | | | |
| | | 9 | 9 | 4 | 9 | 8 | 8 | 0 | 10/7/1999 | WO | | | |
| | | 7 | 3 | 5 | 2 | 5 | 8 | | 11/20/1997 | AU | | | |
| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) | | | | | | | | | | | | | |
| | | U.S. Serial No. 09/671,100, Pinsky et al., Methods for Treating an Ischemic Disorder and Improving Stroke Outcome, filed September 27, 2000 (Exhibit 2). | | | | | | | | | | | |
| | | Benedict C.R., et al. (1994) Endothelial-Dependent Procoagulant and Anticoagulant Mechanisms, Recent Advances in Understanding. Texas Heart Institute Journal 21:86-90. | | | | | | | | | | | |
| | | Bronner et al. (1995) Primary prevention of stroke. The New England J. Med. 333:1392-1400. | | | | | | | | | | | |
| | | Brown and Piantadosi (1992) Recovery of Energy Metabolism in Rat After Carbon Monoxide Hypoxia. J. Clin. Invest. 89:666-672. | | | | | | | | | | | |
| | | Carlos and Harlan (1994) Leukocyte-Endothelial Adhesion Molecules. Blood. 24:2068-2102. | | | | | | | | | | | |
| EXAMINER | | | | | | DATE CONSIDERED | | | | | | | |
| *EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | | | | | | | | | | | | | |

Applicants: David J. Pinsky et al.
 Serial No.: Not Yet Known
 Filed: October 3, 2003
 Exhibit A

| | | | | | | | |
|--|--|--|--|---|--|-----------------------------|--|
| Form PTO-1449 | | U.S. Department of Commerce Patent and Trademark Office | | Atty. Docket No. 51917-CA-PCT-US/ JPW/GIG/DJK | | Serial No. Not Yet Known | |
| INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) | | | | Applicants: David J. Pinsky et al. | | | |
| | | | | Filing Date Herewith | | Group | |
| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) | | | | | | | |
| | | Connolly et al. (1996) Cerebral Protection in Homozygous Null ICAM-1 Mice After Middle Cerebral Artery Occlusion. J. Clin. Invest. 97:209-216. | | | | | |
| | | Connolly et al. (1996) Procedural and Strain-Related Variables Significantly Affect Outcome in a Murine Model of Focal Cerebral Ischemia. Neurosurgery. 38:523-532. | | | | | |
| | | Dawson and Snyder (1994) Gases as biological messengers; nitric oxide and carbon monoxide in the brain. J. Neuroscience. 5147-5159. | | | | | |
| | | Dietrich et al. (1995) Influence of High-Dose Aprotinin on Anticoagulation, Heparin Requirement, and Celite-and Kaolin-Activated Clotting Tie in Heparin-pretreated Patients Undergoing Open-Heart Surgery. Anesthesiology, 83(4) 679-689. | | | | | |
| | | Fassbender et al. (1995) Circulating Selectin-and Immunoglobulin-Type Adhesion Molecules in Acute Ischemic Stroke. Stroke. 26:1361-1364. | | | | | |
| | | Fujita, T. et al., (2001) Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by derepression of fibrinolysis. Nature Medicine. 7(5):598-604 (Exhibit 3). | | | | | |
| | | Holdright, D., et al. (1994) Comparison of the Effect of Heparin and Aspirin Versus Aspirin Alone on Transient Myocardial Ischemia and In-hospital Prognosis in Patients With Unstable Angina. J. Am. Coll. Cardiol. 24:39-45. | | | | | |
| | | Iberti, T.J. et al., (1994) Abnormal Coagulation Profile in Brain Tumor Patients During Surgery. Neurosurgery 34:389-395. | | | | | |
| | | Ishimaru et al. (1991) Effects of successive carbon monoxide exposures on delayed neuronal death in mice under the maintenance of normal body temperature. Biochem. Biophys. Res. Comm. 179:836-840. | | | | | |
| | | Jerome et al. (1994) P-selectin and ICAM-1-Dependent Adherence Reactions: Role in the Genesis of Postischemic No-Reflow. Am. J. Physiol. 226:H1316-H1321. | | | | | |
| EXAMINER | | | | DATE CONSIDERED | | | |
| *EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | | | | | | | |

| | | | | | | | |
|--|--|--|--|---|--|-----------------------------|--|
| Form PTO-1449 | | U.S. Department of Commerce Patent and Trademark Office | | Atty. Docket No. 51917-CA-PCT-US/ JPW/GJG/DJK | | Serial No. Not Yet Known | |
| INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) | | | | Applicants: David J. Pinsky et al. | | | |
| | | | | Filing Date Herewith | | Group | |
| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) | | | | | | | |
| | | Kim et al. (1995) Adhesive Glycoproteins CD11a and Cd18 are Upregulated in the Leukocytes from Patients with Ischemic Stroke and Transient Ischemic Attacks. J. Neurol. Sci. 128:45-50. | | | | | |
| | | Kochaneck and Hallenbeck (1992) Polymorphonuclear Leukocytes and Monocytes/Macrophages in the Pathogenesis of Cerebral Ischemia and Stroke. Stroke. 23:1367-1379. | | | | | |
| | | Kuwabara, K. et al., (1995) Calreticulin, an Antithrombotic Agent which Binds to Vitamin K-Dependent Coagulation Factors, Stimulates Endothelial Nitric Oxide Production, and Limits Thrombosis in Canine Coronary Arteries. J. Biol. Chem. 270:8179-8187. | | | | | |
| | | Mayevsky et al. (1995) Multiparametric monitoring of the awake brain exposed to carbon monoxide. J. Appl. Physiol. 78:1188-1196. | | | | | |
| | | Okada et al. (1994) P-selectin and Intercellular Adhesion Molecule-1 Expression After Focal Brain Ischemia and Reperfusion. Stroke. 25:202-211. | | | | | |
| | | Pinsky et al. (1996) Hypoxia-Induced Exocytosis of Endothelial Cell Weibel-Palade Bodies, a Mechanism for Rapid Neutrophil Recruitment After Cardiac Preservation. J. Clin. Invest. 97:493-500. | | | | | |
| | | Schroeter et al. (1994) Local Immune Response in the Rat Cerebral Cortex After Middle Cerebral Artery Occlusion. J. Neuroimmunol. 55:195-203. | | | | | |
| | | Seekamp et al. (1994) Role of Selectins in Local and Remote Tissue Injury Following Ischemia and Reperfusion. Am. J. Pathol. 44:592-598. | | | | | |
| | | Tijburg et al., (1991) Activation of the coagulation mechanism on tumor necrosis factor-stimulated cultured endothelial cells and their extracellular matrix. The role of flow and Factor IX/IXa. J. Biol. Chem. 266:12067-12074. | | | | | |
| | | Verma et al. (1993) Carbon monoxide: a putative neural messenger. Science. 259:381-384. | | | | | |
| EXAMINER | | | | DATE CONSIDERED | | | |
| *EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | | | | | | | |

| | | | | | | | |
|--|--|--|--|---|--|-----------------------------|--|
| Form PTO-1449 | | U.S. Department of Commerce Patent and Trademark Office | | Atty. Docket No. 51917-CA-PCT-US/ JPW/GJG/DJK | | Serial No. Not Yet Known | |
| INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) | | | | Applicants: David J. Pinsky et al. | | | |
| | | | | Filing Date Herewith | | Group | |
| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) | | | | | | | |
| | | Weyrich et al. (1993) In Vivo Neutralization of P-selectin Protects Feline Heart Endothelium in Myocardial Ischemia and Reperfusion Injury. J. Clin. Invest. 91:2620-2629. | | | | | |
| / | | BBC News report, Health segment, April 30, 2001, Deadly gas 'could save lives' (Exhibit 4). | | | | | |
| / | | International Search Report, August 29, 1997 for PCT/US97/08282 (Exhibit 5). | | | | | |
| / | | International Preliminary Examination, April 20, 1998 for PCT/US97/08282 (Exhibit 6). | | | | | |
| / | | Search Report October 27, 2000 from Patent Office regarding European Patent Application No. 97926541.0 (Exhibit 7). | | | | | |
| / | | International Search Report, June 18, 1999 for PCT/US99/07173 (Exhibit 8). | | | | | |
| / | | International Preliminary Examination, January 7, 2000 for PCT/US99/07173 (Exhibit 9). | | | | | |
| / | | Search Report, May 28, 2002 from Patent Office regarding European Patent Application No. 99916264.7 (Exhibit 10). | | | | | |
| / | | International Search Report, February 5, 1998 for PCT/US97/17229 (Exhibit 11). | | | | | |
| / | | Written Opinion September 14, 1998 for PCT/US97/17229 (Exhibit 12). | | | | | |
| / | | International Preliminary Examination, January 8, 1999 for PCT/US97/17229 (Exhibit 13). | | | | | |
| / | | International Search Report, August 4, 1999 for PCT/US99/07175 (Exhibit 14). | | | | | |
| / | | Written Opinion February 3, 2000 for PCT/US99/07175 (Exhibit 15). | | | | | |
| / | | International Preliminary Examination, July 11, 2000 for PCT/US99/07175 (Exhibit 16). | | | | | |
| EXAMINER | | | | DATE CONSIDERED | | | |
| *EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | | | | | | | |